

References

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NOTE: (Medline: 97436610).
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NOTE: (AIDSLINE: 95191011).
- [Bedford (1997)] P. Bedford, L. B. Clarke, G. Hastings, & S. Knight. Primary proliferative responses to peptides of HIV Gag p24. *J AIDS Hum Retrovirology* **14**:301–306, 1997.
NOTE: (Medline: 97265565) 23 overlapping 15 mers peptides from Gag p24 were used to pulse dendritic cells to identify epitopes by stimulating primary proliferative responses *in vitro* from PBMC from healthy HIV-negative donors. Novel responses were detected.
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NOTE: (Medline: 92127899) This gp41 peptide consistently elicits both T-cell blastogenic and B-cell (antibody) responses in asymptomatic HIV-seropositive individuals but not in ARC and AIDS patients. gp41 epitope: LGIWGCSGKLIC.
- [Berzofsky (1988)] J. A. Berzofsky, A. Bensussan, K. B. Cease, J. F. Bourge, R. Cheynier, Z. Lurhama, J.-J. Salaun, R. C. Gallo, G. M. Shearer, & D. Zagury. Antigenic peptides recognized by T lymphocytes from AIDS viral envelope-immune humans. *Nature* **334**:706–708, 1988.
NOTE: (Medline: 88318926) Test of response to synthetic peptides of lymphocytes from 14 healthy human volunteers who had been immunized with a rec vaccinia virus containing HIV gp160, then boosted with a recombinant fragment containing the carboxyl-terminal 40% of gp120. 8/14 showed a proliferative response to T1; 4/14 to T2. A reduced response to T2 in terms of both magnitude and frequency may have been because of the boost containing the region covering T1, but not T2, and because of the timing of sampling relative to immunization. Some HLA typing was done but no conclusive MHC restriction patterns were determined. Env epitopes: T1: KQIINMWQEVGLAMYA and T2: HEDIISLWDQSLK.
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NOTE: (Medline: 96159130).
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NOTE: (AIDSLINE: 92013142) 20% of T-cell clones from individuals inoculated with a recombinant nonglycosylated form of gp120 failed to respond to glycosylated protein. The epitope for one such clone was mapped and contained two glycosylated asparagines. Thus N-linked carbohydrates can abrogate antigen recognition by T lymphocytes.
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NOTE: (Medline: 95314456).

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- NOTE: (Medline: 90229719) Synthetic peptides representing a defined CD4+ human T-cell epitope in gp120 were used to survey gp120 molecules from various HIV-1 strains for the capacity to be recognized in the context of a single human MHC molecule, DR4. gp120 epitope: GSDTITLPCRILKQFINMWQE.
- [Caruso (1997)] A. Caruso, S. Licenziati, A. D. Canaris, M. Corulli, M. A. De Francesco, A. Cantalamessa, F. Fallacara, S. Fiorentini, A. Balsari, & A. Turano. T cells from individuals in advanced stages of HIV-1 infection do not proliferate but express activation antigens in response to HIV-1-specific antigens. *J Acquir Immune Defic Syndr Hum Retrovirol* **15**:61–69, 1997.
- NOTE: (Medline: 97358560).
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- NOTE: (Medline: 87231983) An algorithm based on a model of immunodominant helper T-cell sites forming amphipathic helices was used to identify for the first time two T-cell sites, env T1 and env T2. These two peptides were shown to stimulate proliferation of T-cells in mice immunized with a fragment of the env protein. Also, mice immunized with T1 were able to induce immunity to env gp120. Multiple haplotypes were responsive. Env epitopes: T2: HEDIISLWDQSLK and T1: KQIINMWQEVGKAMYA.
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- NOTE: (Medline: 92259993) Cell-mediated immune response to HIV-1 can be detected in the absence of a humoral immune response in individuals recently exposed to HIV-1. gp160 epitopes: T1, T2, TH4.1, P18-IIIb, P18-MN.
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- NOTE: (Medline: 91170774) Peptides reported to stimulate Th cell function were used to demonstrate CTL activity in a similar patient population. Env epitopes: T1, T2, Th4 and P18.
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- NOTE: (Medline: 89262051) Investigation of the T-helper cell response of 42 asymptomatic HIV-seropositive patients to four synthetic gp160 peptides and to influenza A virus. This paper suggests that a proliferative response is lost in HIV-1 infected individuals prior to the loss of IL-2 production. Env epitopes: T1, T2, TH4.1 and P18.
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- NOTE: (Medline: 91257138) Immunization of uninfected individuals with an HIV subunit vaccine results in stronger Th cell immunity than does natural infection. Boosting enhances helper function. Env epitopes: T1, T2, TH4.1, P18.

[De Groot (1991)] A. S. De Groot, M. Clerici, A. Hosmalin, S. H. Hughes, D. Barnd, C. W. Hendrix, R. Houghten, G. M. Shearer, & J. A. Berzofsky. Human immunodeficiency virus reverse transcriptase T-helper epitopes identified in mice and humans: correlation with a cytotoxic T-cell epitope. *J Infect Dis* **164**:1058–1065, 1991.

NOTE: Medline: 92064980. The peptide CTEMEKEGKISKIGP stimulates both murine helper and cytotoxic T-cells in H-2^k mice, and was able to stimulate IL-2 producing T-cells from 9 out of 17 HIV seropositive humans. Additional murine RT epitopes were identified by peptide stimulation of T-cells cultured from lymph nodes of RT immunized mice.

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NOTE: (AIDSLINE: 92227948) Helper T-cell epitopes in nef were investigated using five synthetic peptides selected for their amphipathic and α helix properties. One of the peptides, 45-59 was very immunogenic, and could induce functional T-cell help *in vivo*.

[Gaudebout (1997)] P. Gaudebout, D. Zeliszewski, J. J. Golvano, C. Pignal, S. Le Gac, F. Borrás-Cuesta, & G. Sterkers. Binding analysis of 95 HIV gp120 peptides to HLA-DR1101 and -DR0401 evidenced many HLA-class II binding regions on gp120 and suggested several promiscuous regions. *J Acquir Immune Defic Syndr Hum Retrovirol* **14**(2):91–101, 1997.

NOTE: (Medline: 97205213).

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NOTE: (Medline: 90302545) In this study, mice were immunized with multivalent peptides anchored in a phospholipid complex; these peptides were able to stimulate a potent antibody response. That a functional T-helper cell epitope is present within the peptide is inferred by the ability of B-cells to respond to these constructs. Using this system, adjuvant could be bypassed.

[Haas (1991)] G. Haas, R. David, R. Frank, H. Gausepohl, C. Devaux, J.-M. Claverie, & M. Pierres. Identification of a major human immunodeficiency virus-1 reverse transcriptase epitope recognized by mouse CD4+ T lymphocytes. *Eur J Immunol* **21**:1371–1377, 1991.

NOTE: (Medline: 91257142) RT peptides were recognized by several of the T-helper lines established from RT-primed mice. Further, T-cells from peptide-primed mice could be restimulated by native RT. RT epitope: KEKVYLA WVP AHKGIG.

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NOTE: (Medline: 91207940) Six helper T multideterminant regions of the HIV envelope protein are recognized by mice of either three or all four murine MHC types.

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NOTE: (Medline: 97261640).

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NOTE: (Medline: 93171812) In this study the immunogenicity of a T1-V3 loop hybrid peptide in chimpanzees was dramatically reduced by the addition of the gp41 fusogenic domain to the hybrid peptide. This was hypothesized to be the result of the HIV gp41 fusion domain having an immunoregulatory function *in vivo*, that results in primate immune hyporesponsiveness to otherwise immunogenic peptides.

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NOTE: (Medline: 97332393).

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NOTE: (Medline: 91132039) Induction of T-cell help in rhesus monkeys *Macaca mulatta* by priming with peptides T2 or TH4.1 enhances antibody response to a subsequent suboptimal gp160 immunization. T1 alone failed to elicit a response in these experiments. Env epitopes: T1, T2, TH4.1.

[Klinman (1995)] D. M. Klinman, B. F. Haynes, & J. Conover. Activation of interleukin 4- and interleukin 6-secreting cells by HIV-specific synthetic peptides. *AIDS Res Hum Retroviruses* **11**:97–105, 1995.

NOTE: (AIDSLINE: 95251942) Immunized mice activate IL-4 and IL-6 producing cells in a dose dependent manner. The V3 region epitope as well as the T1 epitope is able to activate cytokine-producing cells. The order of immunization of T1-SP10 peptides influences the magnitude and cross-reactivity of the response, where the SP10, V3 portion of the immunogen is varied.

[Krowka (1990)] J. Krowka, D. Stites, R. Debs, C. Larsen, J. Fedor, E. Brunette, & N. Duzgunes. Lymphocyte proliferative responses to soluble and liposome-conjugated envelope peptides of HIV-1. *J Immunol* **144**:2535–2540, 1990.

NOTE: (Medline: 90203581) Conjugation of HIV peptides or proteins to liposomes and stimulation with rIL-2 may enhance cell-mediated responses to peptides. gp120 epitopes: QIVKKLREQFGNNK, FRPGGGDMRDNRSEL.

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NOTE: (Medline: 97400379).

[Lekutis (1997)] C. Lekutis, J. W. Shiver, M. A. Liu, & N. L. Letvin. HIV-1 env DNA vaccine administered to Rhesus monkeys elicits MHC class II-restricted CD4+ T helper cells that secrete IFN-gamma and TNF-alpha. *J Immunol* **158**:4471–7, 1997.

NOTE: (Medline: 97272168) A Th cell response was elicited by an HIV-1 gp120 plasmid vaccine. All of the CD4+ Th cell lines secreted IFN- gamma and TNF-alpha without appreciable IL-4 production, eliciting a Th1-like immune response.

[Manca (1995a)] F. Manca, D. Fenoglio, M. T. Valle, G. L. Pira, A. Kunkl, R. S. Balderas, R. G. Baccala, D. H. Kono, A. Ferraris, D. Saverino, F. Lancia, L. Lozzi, & A. N. Theofilopoulos. Human T helper cells specific for HIV reverse transcriptase: possible role in intrastructural help for HIV envelope-specific antibodies. *Eur J Immunol* **25**:1217–1223, 1995a.

NOTE: (Medline: 95293014).

[Manca (1995b)] F. Manca, D. Fenoglio, M. T. Valle, G. L. Pira, A. Kunkl, A. Ferraris, D. Saverino, F. Lancia, L. Mortara, L. Lozzi, M. Pierres, A. G. Dalgleish, & G. Lewis. Human CD4+ T cells can discriminate the molecular and structural context of T epitopes of HIV gp120 and HIV p66. *J AIDS* **9**:227–237, 1995b.

NOTE: (Medline: 95308197) *In vitro* priming with peptides often induced CD4+ T-cells that did not recognize whole protein. Priming with protein did not always induce T-cells that could be recognized in the context of the virus.

[Manca (1996)] F. Manca, P. D. P., D. Fenoglio, M. N. Ombra, G. Li Pira, D. Saverino, M. Autiero, L. Lozzi, L. Bracci, & J. Guardiola. Antigenicity of HIV-derived T helper determinants in the context of carrier recombinant proteins: effect on T helper cell repertoire selection. *Eur J Immunol* **26**:2461–9, 1996.

NOTE: (Medline: 97054664) A given Th epitope was recognized by a specific T cell clone only when it was inserted in a particular position of the carrier, and the permissive position was not the same for all epitopes.

[Manca (1993)] F. Manca, E. Seravalli, M. T. Valle, D. Fenoglio, A. Kunkl, G. L. Pira, S. Zolla-Pazner, & F. Celada. Non-covalent complexes of HIV gp120 with CD4 and/or mAbs enhance activation of gp120-specific T clones and provide intermolecular help for anti-CD4 antibody production. *Internatl Immunol* **5**:1109–1117, 1993.

NOTE: (AIDSLINE: 94059863).

[Mills (1990)] K. H. G. Mills, A. L. Barnard, B. P. Mahon, P. A. Kitchin, S. E. Adams, S. M. Kingsman, & A. J. Kingsman. Induction of HIV-specific immune responses in primates: fine specificity of antibody and helper T-cell recognition of the HIV p24 protein. *Vaccines* **90**:213–218, 1990.

NOTE: Four cynomolgous macaques were immunized with 3 doses of p24 TY virus-like particles and their immune response was followed. Three 15 mer peptides stimulated CD4 T-cells proliferation and IL-2 production. Two of these responses were verified at the clonal level. B-cell responses were also studied in this paper.

[Mutch (1994)] D. Mutch, J. Underwood, M. Geysen, & S. Rodda. Comprehensive T-Cell epitope mapping of HIV-1 *env* antigens reveals many areas recognized by HIV-1-seropositive and by low-risk HIV-1-seronegative individuals. *J. of Acquired Immune Deficiency Syndromes* **7**:879–890, 1994.

NOTE: (Medline: 94328220) The proliferative T-cell response to pools of overlapping 17 mer peptides spanning Env were tested in both seronegative and low risk seropositive people. The pool that gave the greatest number of responders was pool 25, located in gp41. The 17 mer peptides used in this pool were tested individually for their ability to stimulate T-cell proliferation, and the most critical regions were found to be GIWGCSGKLIC and PWNASWSN. Mutch et al. suggest that the proliferative response in HIV-1 seronegative individuals is more likely due to cross-reactive, non-HIV induced memory cells than naive T-cells.

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NOTE: (Medline: 97304244).

[Nehete (1993)] P. N. Nehete, W. C. Satterfield, C. M. Matherne, R. B. Arlinghaus, & K. J. Sastry. Induction of human immunodeficiency virus-specific T cell responses in rhesus monkeys by synthetic peptides from gp160. *AIDS Res Hum Retroviruses* **9**:235–40, 1993.

NOTE: (Medline: 93229110) Three rhesus monkeys were immunized with eight synthetic peptides that induce T cell activity in mice. PBMCs from these monkeys were monitored every 2 weeks for 34 weeks for proliferative responses against individual peptides and gp160.

HIV Helper T-cell Epitopes

[Palker (1989)] T. J. Palker, T. J. Matthews, A. Langlois, M. E. Tanner, M. E. Martin, R. M. Searce, J. E. Kim, J. A. Berzofsky, D. P. Bolognesi, & B. F. Haynes. Polyvalent human immunodeficiency virus synthetic immunogen comprised of envelope gp120 T helper cell sites and B-cell neutralization epitopes. *J Immunol* **142**:3612–3619, 1989.

NOTE: (Medline: 89235170) Synthetic peptides containing type-specific neutralizing determinants of the V3 loop of gp120 were coupled to a 16 amino acid T-cell epitope (T1) of HIV-IIIB and used to immunize goats. The helper T-cell epitope T1 could induce both a proliferative response and a B-cell antibody response. Conversely, the B-cell epitope in the V3 region, SP10 was found to stimulate proliferative T-cell responses.

[Pinto (1995)] L. A. Pinto, J. Sullivan, J. A. Berzofsky, M. Clerici, H. A. Kessler, A. L. Landay, & G. M. Shearer. Env-specific cytotoxic T lymphocyte responses in HIV seronegative health care workers occupationally exposed to HIV-contaminated body fluids. *J Clin Invest* **96**:867–876, 1995.

NOTE: (Medline: 95362849) Helper responses were detected in 75% of HIV seronegative health care workers, while only 35% had an HIV specific CTL response.

[Polydefkis (1990)] M. Polydefkis, S. Koenig, C. Flexner, E. Obah, K. Gebo, S. Chakrabarti, P. L. Earl, B. Moss, & R. F. Siliciano. Anchor sequence-dependent endogenous processing of human immunodeficiency virus 1 envelope glycoprotein gp160 for CD4+ T-cell recognition. *J Exp Med* **171**:875–887, 1990.

NOTE: (Medline: 90171850) Human CD4+ T-cell clones and cell lines were shown to lyse recombinant vaccinia virus-infected cells that synthesize the HIV-1 envelope glycoprotein gp160, showing that endogenously processed antigen can be presented by class II MHC. gp160 epitope: GSDTITLPCRKQFINMWQE.

[Ranki (1997)] A. Ranki, J. Suni, V. Blazevic, P. Holmstrom, S. Mattinen, K. Krohn, & S. L. Valle. T-cell recognition of HIV antigens in HIV-seroreverted persons. *AIDS* **11**(1):132–133, 1997.

NOTE: (Medline: 97264223).

[Sarobe (1994)] P. Sarobe, J.-J. Lasarte, I. Prieto, A. Gullon, M.-J. Soto, P. Labarga, J. Prieto, & F. Borrás-Cuesta. Induction of neutralizing antibodies against human immunodeficiency virus type 1 using synthetic peptide constructs containing an immunodominant T-helper cell determinant from vpr. *J AIDS* **7**:635–640, 1994.

NOTE: (AIDSLINE: 94267704) A vpr peptide was shown to stimulate a T-cell proliferative response in 37% of HIV+ individuals. This peptide was coupled with B-cell epitopes, and immunized mice were capable of antibody production.

[Sastry & Arlinghaus(1991)] K. J. Sastry & R. B. Arlinghaus. Identification of T-cell epitopes without B-cell activity in the first and second conserved regions of the HIV Env protein. *AIDS* **5**:699–707, 1991.

NOTE: (Medline: 91354553) Seven out of 19 peptides induced good T-cell proliferative response in mice representing four major histocompatibility complex haplotypes, without eliciting an Ab response. Eleven peptides were able to induce T-cells that could proliferate in response to recombinant gp160 (greater than or equal to 3 fold relative to unrelated peptides). Peptides were modified to generate polymers with disulfide bonds or micelles with palmitic acid residues attached to the amino-terminal lysine; in these configurations peptides were immunogenic without being coupled to a carrier molecule. F1 hybrid mice were used: ASW x BALBc F1 (H-2^{kxb}) and B6C3 F1 (H-2^{sxd}).

[Schrier (1989)] R. D. Schrier, J. W. Gnann Jr., R. Landes, C. Lockshin, D. Richman, A. McCutchan, C. Kennedy, M. B. A. Oldstone, & J. A. Nelson. T-cell recognition of HIV synthetic peptides in a natural infection. *J Immunol* **142**:1166–1176, 1989.

NOTE: (Medline: 89124356) The ability of 21 peptides to stimulate T-cell proliferation was tested in 30 HIV-infected donors in different clinical stages. T-cells from 27/30 donors were able to respond to at least one peptide. Two of the peptides were able to stimulate proliferation in 48% of the donors. Schrier et al. did not write down the peptide sequences they used, but only provided the numbering of the boundaries on a reference sequence (LAI, Wain-Hobson et al., Cell 40:9-17 (1985)). In our experience, such numbering is often imprecise, so the peptide assignments in this database may be off by several residues. Two epitopes that Schrier et al. mistakenly labeled as p24 peptides are instead p15 peptides.

[Schrier (1988)] R. D. Schrier, J. W. Gnann Jr., A. J. Langlois, K. Shriver, J. A. Nelson, & M. B. A. Oldstone. B- and T-lymphocyte responses to an immunodominant epitope of human immunodeficiency virus. *J Virol* **62**:2531–2536, 1988.

NOTE: (Medline: 88275015) Characterization of murine T-lymphocyte dependent B-cell responses; also, T-cells from 7/29 HIV-1 positive people showed a proliferative response to this peptide.

[Shirai (1996)] M. Shirai, M. Chen, T. Arichi, T. Masaki, M. Nishioka, M. Newman, T. Nakazawa, S. M. Feinstone, & J. A. Berzofsky. Use of intrinsic and extrinsic helper epitopes for in vivo induction of anti-hepatitis C virus cytotoxic T lymphocytes (CTL) with CTL epitope peptide vaccines. *J Inf Dis* **173**:24–31, 1996.

NOTE: (AIDSLINE: 96132459).

[Sjolander (1996)] S. Sjolander, A. Bolmstedt, L. Akerblom, P. Horal, S. Olofsson, B. Morein, & A. Sjolander. N-linked glycans in the CD4-binding domain of human immunodeficiency virus type 1 envelope glycoprotein gp160 are essential for the in vivo priming of T cells recognizing an epitope located in their vicinity. *Virology* **215**:124–33, 1996.

NOTE: (Medline: 96146726) An investigation of whether T cell responses to the HIV-1 gp160 were sensitive to deletion of three N-glycans of the protein.

[Takahashi (1990)] H. Takahashi, R. N. Germain, B. Moss, & J. A. Berzofsky. An immunodominant class I-restricted cytotoxic T lymphocyte determinant of human immunodeficiency virus type 1 induces CD4 class II-restricted help for itself. *J Exp Med* **171**:571–576, 1990.

NOTE: (Medline: 90155121) This same epitope can be recognized in the context of a class I MHC D^d, by CD4⁺ CD8⁺ CTL, and in the context of a class II MHC A^d by CD4⁺ CD8⁺ T-helper cells.

[Takeshita (1995)] T. Takeshita, H. Takahashi, S. Kozlowski, J. D. Ahlers, C. D. Pendleton, R. L. Moore, Y. Nakagawa, K. Yokomuro, B. S. Fox, D. H. Margulies, & J. A. Berzofsky. Molecular analysis of the same HIV peptide functionally binding to both a class I and a class II MHC molecule. *J Immunol* **154**:1973–1986, 1995.

NOTE: (AIDSLINE: 95138543) Of RGPGRFAFVTI, the upper case iGPgRaFvtI are critical for for binding, consistent with the H-2Dd motif XGPX(RKH)XXX(X)(LIF). Stimulation of the HLA class II I-A^d required a longer peptide, IQRGPGRFAFVTI or RIQRGPGRFAFVTI, and riqrGPgRaFvti were essential for binding to the Class II molecule.

[Vaslin (1994)] B. Vaslin, J.-M. Claverie, O. Benveniste, F. C. Barre-Sinoussi, & D. Dormont. Nef and gag synthetic peptide priming of antibody responses to HIV type 1 antigens in mice and primates. *AIDS Res Hum Retroviruses* **10**:1241–1250, 1994.

NOTE: (AIDSLINE: 95151361) Four Gag peptides, that when pooled are able to prime for subsequent antibody response to HIV in mice, were studied. These peptides were also able to prime *in vitro* immunoproliferative responses. The two peptides of the four that were able to prime humoral responses to inactivated HIV-1 are included in the table (G2 and G4) – the other two are not included (G1 and G3). Three proposed nef helper T-cell epitopes are also not included in the table, but may be of interest. These nef peptides could prime the humoral response in mice, but not *in vitro* proliferation. Priming was also observed in baboons, using the pool of four Gag peptides.

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NOTE: (AIDSLINE: 95018258).

[Wahren (1989a)] B. Wahren, T. Mathiesen, J. Rosen, & H. Wigzell. Common and unique T-cell epitopes of HIV-1. *Vaccines* **89**:89–93, 1989a.

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[Wahren (1989b)] B. Wahren, J. Rosen, E. Sandstrom, T. Mathiesen, S. Modrow, & H. Wigzell. HIV-1 peptides induce a proliferative response in lymphocytes from infected persons. *J AIDS* **4**:448–456, 1989b.

NOTE: (Medline: 90011749) Using 15-amino-acid-long peptides that scanned all of gp41, the C-terminal half of gp120, and the gag proteins p17, p24, and p15, this study presents evidence that 18 envelope and 12 gag peptides could stimulate T-cell proliferative responses from multiple representatives among 99 HIV infected study subjects. Thirty-six seronegative subjects were used as controls.

[Warren & Thomas(1992)] A. P. Warren & D. B. Thomas. Class II (II-A^d) restricted T-cell recognition of the V3 loop region of HIV-1 gp120. *AIDS Res Hum Retroviruses* **8**:559–564, 1992.

NOTE: (Medline: 92385157) The epitope defined here is the immunodominant epitope for a helper T-cell response to the gp120 vaccine in mice.

[Wasik (1997)] T. J. Wasik, P. P. Jagodzinski, E. M. Hyjek, J. Wustner, G. Trinchieri, H. W. Lischner, & D. Kozbor. Diminished HIV-specific CTL activity is associated with lower type 1 and enhanced type 2 responses to HIV-specific peptides during perinatal HIV infection. *J Immunol* **158** (12):6029–6036, 1997.

NOTE: (Medline: 97334261) Only three out of seven children with rapidly progressing disease had detectable CTL activity, and CTL activity was correlated with a normal Th1 response. Children that did not have a strong CTL response had an increased proportion of Th2 cells relative to Th1.

[Wilson (1997)] S. E. Wilson, J. A. Habeshaw, M. A. Addawe, E. F. Hounsell, & J. S. Oxford. HIV type 1 envelope glycoprotein 120 carboxy-terminal peptide-induced human T cell lines selectively suppress heterogeneous proliferative T cell responses to soluble antigens. *AIDS Res Hum Retro* **13**(15):1313–1324, 1997.

NOTE: (Medline: 97479767).